

The Neuroanalyst

Brain Profiling for Psychiatric Diagnosis

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"Diagnose the brain disturbance of your patient!"

Glossary

CBP = Clinical Brain Profiling

DDMN = Disturbances to the Default Mode Network

DMDD = Disturbance of matching-dynamics of the de-optimized type

DMDD_rnr = Disturbance of matching-dynamics of the de-optimized type due to reduced neural resilience

DMDD_ea = Disturbance of matching-dynamics of the de-optimized type due to environmental alteration

DMDDo = Disturbance of matching-dynamics of the optimized type

DMCO = Disturbance to multiple constraint organization

ibDMCO = Input-bound disturbance to multiple constraint organization

DD = Disconnection dynamics

TDS = Top-down shift

OD = Over-connectivity dynamics

BUI = Bottom-up insufficiency

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Introduction:

The taxonomy of the DSM is not brain-related and thus disconnects clinical psychiatry from its etiopathological neuroscientific origins. This manual reconceptualizes mental disorders as brain disorders by introducing insights from computational neuroscience, a discipline in a position to explain brain disorganization and thus offers a valid methodical foundation for understanding mental disorders.

The major achievement of the DSM was in reaching reliability. This was achieved by consensus, now it is time to reach validity. To do so, a brain-related formulation of mental disorders is critical. Fear of compromising reliability again hinders any modification of the DSM taxonomy, however since any taxonomy can be reliable based on consensus, a novel brain-related conceptualization of mental disorders can also achieve reliability, with the advantage that brain-related taxonomy can be validated.

By reformulating mental disorders using Clinical Brain Profiling (CBP) we lay the ground for medical, etiopathologically based psychiatry disorders that have the potential for targeted treatments.

Here a concise set of summaries exemplify how to translate your clinical findings at the bedside into a formulation of patient-specific brain disturbances. This manual focuses on rapid clinical assessment for the

patient. It is based on broader in depth literature (Peled 1999a, 1999b, 2008, 2010) that is briefly discussed in this manual.

The CBP diagnosis of the patient can be nominally explained in the various sections, appendix 1 dictionary and summarized in Table 1 or it can be measured using a vector in which entries represent the percent of the average of symptom-collections over all possible symptom signs and history findings (Appendix 2). The first approach of nominal translation is detailed in the dictionary of appendix 1, it has the advantage of introducing a neuroscientific nomenclature currently lacking, for mental disorders. The neuroscientific outlook of appendix 1 is advantageous in its ability to induce psychiatrists to ask the relevant questions toward finding the etiology of mental disorders, and it is also useful in bringing psychiatry back to a scientific brain-related discipline of mental disorders. Finally CBP is less stigmatizing than the descriptive diagnosis where the patient is "defective." Here the brain of the patient is the organ of disturbance just as the heart is malfunctioning in cardiac diseases and other organs are deficient in internal medicine.

In using a vector-based CBP formulation all the major brain disturbances constitute the entries of the vector, thus the vector is constructed as follows DDMN, DMDd, DMDo, DMCO, ibDMCO, DD, TDS, OD, BUI (see Table 1 and appendix 1 dictionary for details). Each entry is a number representing the percentage of relevant symptom manifestations from all possible symptom signs and history for all mental disorders. A translation matrix (see Appendix 2) implemented in a computer program is available at www.neuroanalysis.org.il for computing the CBP parameters. The vector-

based CBP is useful for imaging and epidemiology research; it is also valuable for assessing treatment response and is critical for appropriate research seeking the causes of mental disorders.

Background

Today treating patients with disturbances of high mental function is a patchy business. Psychologists, psychiatrists and neurologists all are involved in treating those suffering from behavioral, cognitive, and emotional irregularities, as well as other disturbances of maladaptive debilitating consequences.

While most agree on the central role of brain disturbances in mental disorders, psychologists go about treating them based on general theoretical conjectures (such as ‘defense Mechanisms,’ ‘drives,’ and object relationships) that are not brain related. Neurologists constrain themselves to macroscopically identifiable tissue damage that explain only certain well-defined brain disturbances (typically of a lower-level such as motor sensory conduction and certain straight-forward cognitive functions).

Psychiatrists are positioned in-between; on the one hand psychiatry research is directed toward molecular and genetic levels of brain functions, and on the other hand psychiatrists use non-brain-related descriptive diagnostic taxonomy disengaging the brain from clinical phenomenology (Peled 2008).

Why do we have such a fragmented approach when coming to conceptualize and treat patients with mental disorders?

It is typically argued that lack of knowledge about the brain and higher mental functions is responsible for such scientific disarray. But is that true? Are we really confronted by a lack of knowledge or perhaps the available knowledge has not been sufficiently integrated to explain mental disorders? Can such integration create a comprehensive unifying brain-based medical discipline that will collapse neurology psychiatry and psychology into one genuine medical-discipline that will effectively define and treat mental disorders?

In this editorial I will argue that we have the relevant knowledge to unify neurology psychiatry and psychology, I will name this new unified medicine of the brain "NeuroAnalysis" and present an overview of its scientific foundations.

NeuroAnalysis is based on the most fundamental character of the brain, its "Complexity;" - the brain is a complex physical system, composed of billions of interacting neurons, that form highly dynamic ever-changing neuronal network activations and deactivations. As such any clinical science of mental disorders that is not based on complex dynamic systems approach, is plain wrong.

Before any discussion of NeuroAnalysis and mental disorders can begin one has to solve the psychophysical problem and get rid of the unscientific meaningless term of “psyche.” Mental phenomena such as consciousness, awareness and feelings are emergent properties of brain complexity (King 1991) just as liquids are wet, and wetness is not a characteristic of any single water molecule, so is consciousness a whole brain phenomenon not applicable to one neuron, synapse or neurotransmitter. “The whole is more than the sum of parts,” typically describes “Emergent Properties.” What philosophers call 'mind,' 'psyche' and soul are actually emergent properties of brain organization.

What are the characteristics of the complex system that we find in the brain? These are mainly two inter-dependent related characteristics 1) hierarchy and 2) balanced order. Being non-linear (having no trivial linear cause-and-effect relationship) the brain functions on the edge of chaos, meaning that it is balanced between randomness and orderliness, thus the balance of order in the brain is achieved by connectivity dynamics maintaining the brain organization balanced between ‘disconnectivity’ and ‘over-connectivity.’ When disconnectivity prevails, conscious experience fragments and psychotic phenomena take over. When overconnectivity prevails brain dynamics crystallize, freeze (i.e., limiting all brain activity) reducing cognition and thought as is typical to negative signs in schizophrenia or the hypofrontality syndrome (Yoon et al 2008).

The brain is hierarchical; percepts are processed independently and effectively (protected from interferences due to segregation) at the base of the hierarchy and become integrated into complex coherent conscious experiences at the higher levels of brain hierarchy (Baars 1988). Unimodal processes integrate into global transmodal global processes (Mesulam 1998) that offer the global workspace (Baars 1988) from which conscious experiences emerge. Global transmodal organizations are serial network activations composed of partial unimodal processes (smaller network compositions) that join and disjoin the global network in ever-changing parallel activations allowing for the flexibility of cognition and the serially ordered conscious experience. Delusions and illusions are possible when top-down bottom-up balances within the hierarchy are perturbed (Peled 2009).

The brain develops as a network system. We have known this since the mid 19th century when Meynert (1885) said that experiences, thoughts and ideas are encoded within some basic neuronal connectivity formations which he termed 'EGO' (Freud was a student in his department and took the idea from him, developing it theoretically thus disengaging it from the brain). Donald Hebb (1949) conceptualized synaptic plasticity for network formation using the famous declaration about "fire together wire together." Psychologists were wise to appreciate how developmental processes shape internal representations of the psychosocial world calling them "object relationships." Object relationships are critical explanations regarding the way we experience our psychosocial environment, thus our personality styles. Object relationships are internal maps according to which one evaluates and

experiences occurrences and accordingly reacts and adapts to them (Rogers 1965). Today we know that the default-mode-network is probably the Ego as initially conceptualized by Meynert (Carhart-Harris and Friston 2010). We know that networks can incorporate information thus they hold internal maps used as perceptual guidance and interpretation (Rumelhart 1986). So by combining all of the components it becomes obvious that the structure and function of the default mode network is responsible for the way we interpret and react to our environment/external stimuli thus our personality traits. This assumption is exciting because the day that personality disorders will be diagnosed as disturbances to the default mode network is near. An optimal default-mode-network has a measurable organization of small-world-network (i.e., high clustering and short path length (Liu 2008)) measurable via combined signal processing and imaging technology. Thus it is proposed that in personality disorders the normal small-world-network parameter will be altered indicating a disturbed, undeveloped or biased network organization of the personality disorder (Peled 2009).

At the beginning of this editorial 'emergent properties' were introduced to explain higher mental phenomena; mood is certainly such an emergent property. But what specific type of brain dynamics emerges as mood? And what brain dynamics distinguish between depression, mood-elevation and anxiety? To answer these questions let us gather the relevant information available to us with respect to mood and anxiety disorders.

First, we know that effective treatment of mood disorders involves SSRI's (serotonin-specific reuptake inhibitors) and ECT (electroconvulsive therapy) both have to do with distributed whole brain interventions (serotonin is a neurotransmitter of a large percentage of cortical neurons and ECT involves generalized seizures) this whole-brain intervention concords with the idea of emergent properties effects. Second, we know that both SSRI's and ECT are synaptogenetic, increasing the number of dendrites and spines of the neurons spread in the cortex (Pitinger et al 2008). We can conclude that a brain treated with antidepressants is more plastic and changeable due to increased neuronal resilience and augmented capacity to form and change connections within distributed networks.

The plastic brain adapts better to ever-changing environmental occurrences. Such adaptation 'optimizes' the 'match' between the internal representations of the default mode network (Tononi 1996) since stress always involves abrupt changes in the environment (loss of a loved-one, loss of a job etc..) than the plastic brain. Being more flexible, it is better equipped to deal with these changes. The environment is in constant dynamic change, thus the match between the internal representations and external occurrences is never optimal, but constantly moves between more optimal and less optimal conditions. It is not the scope of this editorial to detail 'optimization theory' but it will be assumed that mood is an emergent property of optimization dynamics in the brain, thus deoptimization (when there is a mismatch between internal and external configurations) results in depressed mood and antidepressant effects (and mania) result from optimization dynamics.

Largely unstable (connectivity-wise) networks result in another emergent property, that of anxiety.

The above optimization-theory of mood and anxiety disorders explains many puzzling clinical manifestations, for example so-called 'reactive' versus 'endogenic' depression, with optimization theory it is evident that these two clinical manifestations are two sides of the same brain dynamics. Reduced brain plasticity (from damage, hormonal and other causes) causes deoptimization dynamics and explains 'endogenic depression,' while deoptimization from increased changes in the environment (i.e., stress) also causes deoptimization (mismatch) dynamics and emergence of 'reactive depression.' Anxiety is another clinical manifestation involving optimization-stability network dynamic theory. Anxiety and depression often appear together in many patients, and patients suffering from personality disorders also typically reveal anxiety symptoms. When networks are non-adaptive and deoptimized they become unstable and such instability results in the emergent property of anxiety, explaining the common finding of anxiety in many, if not most, mental disorders.

After considering the above advances in our field we can answer the initial question and affirm that we do have enough knowledge for a novel science of 'NeuroAnalysis.' Accordingly it is time to dispose of non-brain descriptive psychiatry and adopt brain-related neuroscientific psychiatry, where 'personality disorders' are 'disturbances to the default-mode-network,' mood and anxiety disorders are disturbances to 'optimization dynamics' and

schizophrenia-spectrum disorders are disturbances to the connectivity (including hierarchical) balances.

Table 1 summarizes the proposed neuroanalytic brain-based taxonomy for psychiatric diagnosis

Table 1

<i>Disturbance of Brain dynamic</i>	<i>Assumed clinical correlate</i>
Disturbance of default mode network	Personality disorders
Disturbance of optimization dynamics deoptimized type	Symptoms and signs of depression
Disturbance of optimization dynamics hyper-optimization type	Symptoms and signs of mania
Disturbance of optimization dynamics constrain frustration type	Symptoms and signs of anxiety
Dis-connectivity dynamics	Psychosis and positive signs schizophrenia
Over-connectivity dynamics	Repetitive poverty ideation perseverations
Hierarchical insufficiency	Avolition and negative signs schizophrenia
Hierarchical top-down dominance	Systemized organized delusions

Although NeuroAnalysis taxonomy is ready for use (Peled 2009), two challenges deter its final acceptance. First a translation from current descriptive phenomenological taxonomy to brain-related conceptualizations is warranted, and translational matrices can achieve this. For example there is an open access matrix for Clinical Brain Profiling (Peled 2010) available on the web (<http://neuroanalysis.org.il/>). Second, systematic validation of the above must be finalized. Many recently published studies point in the direction of NeuroAnalysis however they do not expressly validate it.

The definitive test and the direct result of a successful NeuroAnalysis should manifest in the clinical arena by the development of effective meaningful therapeutic achievements. The Neuroanalyst will have two major roads to optimize and correct brain disturbances. The first road will involve direct intervention into brain tissue, this will involve relevant plasticity inducing procedures starting from synaptogenerating medications and will also include a range of electro-magneto stimulations cleverly synchronized with corrective disease-related brain network activity. Optogenesis (Peled 2011) will most likely play a critical role in this type of intervention.

The second road is that of experience-dependent-plasticity. According to the NeuroAnalysis approach the currently available range of psychotherapeutic approaches (from short to long, and from behavioral to dynamic insight-oriented) can be considered experience-dependent-plasticity interventions. Their practice will need to adapt to certain standardization and modification to suite the Neuroanalytic perspectives and research findings as they

progress. Newer interventions will be developed using brain-computer interfaces, for example 'Virtual Realty' and Immersive experience (Presence) tailored to create a therapeutic effect based on the neuroanalytic diagnosis.

These two roads will be combined by the Neuroanalyst based on the assumption that correcting brain organization and eliminating aberrant networks will require both the alteration of brain plasticity as well as the desired corrective intervention applied from the external environment.

To be efficient the Neuroanalyst will be trained as a medical doctor and will supplement expertise in non-linear dynamics, computational neuroscience, and signal processing with systems-control sciences. Such difficult training will position the NeuroAnalysts at the pinnacle of medical science.

Section 1: Socially-maladaptive character disordered patients and disturbances of the Default Mode Network.

Though these patients vary in age, they are generally young adults. They come to the psychiatrist for a large range of complaints typically within the range of depression and anxiety, sometimes complaints include low self esteem, the quest to be more assertive, and in other cases they ask for help with inter-personal relationships at work and in coping with matrimonial, couple and family problems.

In more severe cases (e.g., called Borderline organization by psychologists) their histories show patterns of unstable work and interpersonal activity, typically erratic overly attached relationships that quickly turn to rejection and so forth repeating intensive attraction-rejection attitudes. At work this manifests by holding jobs for short periods only, with the consequent financial outcomes of deficits. In personal relationships the intensive attraction-rejection attitudes impedes long-lasting stable relationships, the patient finds himself alone and secluded for long periods.

Less severe cases, such as those typically termed "narcissistic" by psychologists, are overly sensitive to criticism, and over-value what others think of them. They crave for attention and are unable to cope with rejection, an undemanding remark from a superior at work is experienced as humiliating disparagement, and a casual comment from a friend may be interpreted as resentment. These behaviors appear in the clinical history as

inability to maintain stable interpersonal relationships, maintain a job or pursue a career.

Object relationship psychologists refer to personality as reflected from internal representations which they call "Objects." Objects are the representations of other persons, especially those relevant to us that we encounter every day. The internal representation of how we view ourselves is also an "object" internally represented; it is the "Self Object." The relationships between objects are internally-represented-experiences we had with these people in the past, emotional experience is also internalized and incorporated in these internal constructs. The internal constructs of object relations act as "maps" that are activated during incoming stimuli from psychosocial occurrences and the activated map determines the way we experience these occurrences. Thus it is reasonable to conclude that internal representations will determine the way we experience various situations and decide how we react and feel about them.

In short, past experience determines the formation of internal representations according to which new experience is perceived, it is an ongoing developmental dynamic process. Psychologists were quick to understand that these internal formations have critical periods of development; naturally the initial phases of development (infancy childhood) in which the internal constructs are just beginning to form are fundamental to later development and maturation of these internal maps. Proper mature "maps" will "equip" the

adult with the complex flexible adaptable "charts" and "schemes" to cope with everyday psychosocial challenges.

The rule in these cases is that proper investigation of developmental history and past early relationships will reveal problems in child-parent interactions. As already mentioned, early phases of objects formation are critical to the later maturation of the internal constructs or "maps." In severe cases these relationships could be so inconsistent and erratic that the basis for a mature internal representation is totally lacking. The history for such patients will typically reveal disturbed shattered homes that were unable to provide for the consistent care the child needs. This clinical history often corresponds with findings that exemplify chaotic unstable interpersonal relationships at work and within all other social relationships. In less severe cases clinical history may reveal that the relevant parental figure was either over-protective or inversely neglecting and ignoring. In the first case, over-protective attitudes in which the child is the center of attention gives the child the notion of entitlement, and by protecting him from any distress or painful experience leaves him lacking the capacity to cope with disappointment and precludes the formation of internally-constructed coping "maps" for frustration. In the second case, that of the neglecting and ignoring parent, the child is left with cravings for affection, and is sensitive to further rejections. In any case these patients have in common a history of deficient careers and unstable interpersonal relationships that are related to feelings of lack of affection, low self esteem, and over-sensitivity to criticism and disapproval.

Using the above conceptualizations, personality disorders are associated with immature rudimental or biased internal representations. Consequent to these distorted internal representations distress within interpersonal and employment domains ensue. This distress is typically presented to the therapist as depressed and anxious mood, thus depression and anxiety are the chief complaints of patients with personality disorders. The rule in these cases of personality disorders is that complaints of depression and anxiety always have an underlying character problem of interpersonal relationships related to the way others and themselves are psychosocially perceived. It is a biased perception which is reacted upon and which causes maladaptive incongruent reactions.

The idea of a mature flexible adaptive personality has been related in psychology to the concept of "Ego", and personality disorders were related to Ego disturbances (Freud 1956). The term Ego was developed by Freud but originated by Meynert who was Freud's mentor. Meynert used this term to describe brain connectivity organization, claiming a personal individual neural network responsible for representing the experience and thoughts of the individual (Meynert 1968). Modern neuroscience validated this notion of basic connectivity organization in the brain when the default mode network (DMN) was discovered. This is a resting state network activity identified with imaging studies. Recently the relationships between the psychological description of the ego and the formation of the DMN have been scientifically overviewed (Carhart & Friston 2010) making a convincing claim that the DMN can represent Ego formations.

Once connectivity formations represent basic brain organization, it is reasonable to presume that such a connectivity construct is capable of internal representations such as those described by object-relationship psychologists. The ability of connectivity systems to store and manipulate information is at the basis of a rapidly-developing science called "neural computations" where brain simulations are used for computers of artificial intelligence (Rumelhart & McClelland 1986). The idea of parallel distributed processing (PDP) explains how internal representations can be achieved by activations of neural network in the brain. Such activations relate to connection strengths among the synapses of these neuronal ensembles determining the likelihood of their concordant activations (Herz & Krog 1991). Changes in connection strengths are often denominated using the term of "plasticity". Donald Hebb (1949) said that when neurons fire together they wire together, meaning that repeated activations of neuronal ensembles cause the connections between the neurons of that ensemble to become stronger. Since the activated ensemble represents information, the connectivity-formations are the basic mechanisms of learning and memory (Rumelhart & McClelland 1986). This is because once strengthened, the connections facilitate the mutual neuronal activations of the relevant neuronal ensemble, making it "easier" for it to become active thus evoking the information embedded in it.

As mentioned above, psychologists argue that experience determines our internal representations of object relationships. We can now see how experience-dependent-plasticity embeds information memories and

representations in the neural networks of the brain. Repeated experiences cause repeated neuronal-ensemble activation. This forms strong connections within that ensemble, the strengthened connections facilitate the neuronal-ensemble activation and formation, thus it is reasonable to say that the brain organizes by experience (Hebb 1949).

As a result of the above knowledge, we are in a position to reconceptualize personality disorders as disorders of DMN organization and development. Patients with personality disorders are expected to have deficient DMN organization; deficient connectivity organization will be accompanied by deficient constructs of internal presentations. Such deficiency results from alterations and biases of experience-dependent-plasticity, an erratic environment of a shattered family will not be able to provide the repeated stable environmental stimuli responsible for Hebbian activation and favorable experience-dependent plasticity.

A testable prediction for a brain-related cause of personality disorder is that of immature undeveloped and unstable DMN formations in the brains of these patients. Validation of this hypothesis awaits the envelopment of imaging signal processing methods sensitive enough to detect the changes of plasticity and neuronal activations in these patients.

Section 2: Mood and anxiety disorders and disturbances of matching-dynamics and constraint-frustration networks.

The phenomenology of depression and mania is pretty-much straight forward and is outlined extensively in the various DSMs. A challenge for any theory of mood disturbances is to explain the long known dichotomy between "endogenic" depression and "reactive" depression (major depression and the various adjustment DSM-related disorders), to explain bipolar disorders and to explain why patients suffering from personality disorders typically complain of depression and anxiety. Explanations for anxiety and why it typically accompanies depression and many other mental disorders is also warranted.

We know today that antidepressant medication is synaptogenetic, increasing neuronal growth, dendrite arborization and spine formation. These changes increase neuronal resilience and plasticity making vast brain systems more flexible and adaptable (Pittenger, & Duman 2008). Concordantly we know that depression is correlated with neuronal death and cortical atrophy (Drevets et al 2008).

In the previous section we have seen how internal representations are formed from interaction with environmental occurrences; since the world is dynamic, external events continuously alter and change. Internal representations keep pace with these changes by modifying internal formations accordingly, thus reducing the differences between the external occurrences and the internal

representations (Free energy reductions see Friston & Klass 2007), however there is always a continuous mismatch between environmental occurrences and internal representations. This is due to time-lags in adaptation; brain plasticity is typically slower than the events it encodes.

The mismatch between the brain and the environmental occurrences (entailing increased free energy (Friston and Klass 2007) can grow when either the neuronal system is not flexible enough or if the environmental occurrences become erratic with many sudden changes. Hampered neuronal resilience will make the brain system less adaptable to the environmental occurrences increasing the mismatch dynamics between the brain and the environmental occurrences. From this we may assume that if depression arises from neuronal death and neural death causes reduced ability of the brain networks to adapt to the environmental changes entailing mismatch dynamics between the brain and environmental occurrences, then such mismatch dynamics will be manifested as depressed mood. On the contrary good matching dynamics will have an antidepressant mood-elevating effect. The increased neural resilience of antidepressants induces better plasticity to the system, which adapts better to the environmental occurrences increasing matching between the brain and the environment thus elevating mood sensation.

It is emphasized that the relationship between a dynamic change in a physical system such as the brain and a psychological sensation such as mood is understandable using the concept of an "emergent property". Emergent

property is the expression for mental phenomena arising from physical systems, meaning that the whole is more than the sum of the parts, e.g., depressed mood is not a phenomenon of one neuron or one neuro-transmitter it is an emergent property of whole brain dynamics.

As mentioned above, a challenge for any theory of mood disturbances is to explain the long known dichotomy between "endogenic" depression and "reactive" depression. The matching dynamics approach solves this problem; endogenic depression is caused by inability of brain networks to adapt to the regular alterations of environmental occurrences resulting in increased mismatch dynamics between these systems. This happens when metabolic hormonal and neuronal factors impede neural resilience in support of that we know that for example hypothyroidism and dementia are associated with depression. Reactive depression is related to stress, and stress always entails some drastic change in the environment, a dear person dies, a natural catastrophe, etc. all these can exemplify how stress and change of regular input correspond. Erratic environmental occurrences are the basis of any stress and being irregular changes they increase the mismatch between the imputed occurrences and the internal representations that are attempting to adapt to them. The mismatch dynamics which results from this is responsible for the depressed mood that is associated with any reaction to stress.

The explanation for bipolar disorders is linked to oscillations of matching dynamics; such dynamics will have the emergent property of bipolar mood disturbances.

From the above we can deduce why patients suffering from personality disorders typically complain of depression. As explained in the first section these patients suffer from undeveloped biased internal representations, as such they a-priori do not have good matching dynamics with the environmental occurrences, in effect they can never achieve good matching dynamics with the environmental occurrences because inherently being undeveloped and biased they are always different and in contrast to the psychosocial environment. This long lasting incoherence and mismatch arises in the form of milder but long-lasting fluctuating depressed mood (DSM dysthymia).

Network organization of the brain achieves an overall multiple constraint organization (Peled 1999) with that the activity of one neuron constrains the activity of the neuron connected with it. In effect each neuron is bound by the activity of many neurons connected with it and cannot assume any state that is not a multiple constrained state of all the others. As a whole the network is stabilized by these multiple constraint dynamics. If the network becomes unstable the multiple constraint organization can be altered to the extent that neurons will assume independent values of activity that disrupt the overall constraint satisfactions risking disconnection of neuronal activities and pushing the system toward disconnection dynamics. But before such a breakdown occurs it can be assumed that the system is "elastic" enough to absorb a certain level of "frustration" to the constraints. Frustration means that the activity of one neuron in respect to another connected to it does not

fully satisfy the regular transmission values that should have been achieved if the system was regularly stable.

It is argued that frustration of constraints in unstable networks is expressed by the sensation of anxiety as an emergent property of perturbed unbalanced neural networks within the brain. It is reasonable to assume that any type of neuronal computation that requires changes in the activity of brain networks will be accompanied with a certain level of frustration to the network connections, thus inducing some anxiety (existential anxiety). Increased loads of activity such as activity of experience-dependent-plasticity or matching dynamics can increase constraint-frustrations, destabilizing the network and increasing anxiety. If the dynamic alterations surpass certain levels and cause serious network destabilizations then full-blown panic attacks or other anxious syndromes may take place, always as an emergent property of whole brain dynamics, and thus has to involve vast networks spread in the cortex. Certain experiences with their relevant input patterns of brain activations may "resonate" with certain internal representations that when activated may trigger a distributed network destabilization and constraint frustrations. These input-bound destabilizations constitute the clinical phenomenology of phobia, as they are directly related to a triggering event or object.

It is now clear why many mental disorders are accompanied by anxiety in addition to their relevant symptoms. This is because many, if not all, of the mental disorders have to do with certain levels of neural network instability.

Section 3: The seriously disorganized, reality-distorting, cognitively impaired patients and disturbances to connectivity dynamics

These patients are typically presented to the psychiatrist by family members as the patient is reluctant to seek help and if present is non-cooperative. They are young (early adulthood), usually restless and seem distracted and disoriented. On examination patient history reveals a gradual but a short period of transformation from normal behavior into an odd bizarre conduct which is typically conveyed as "the patient is not his regular self." Soon it will become clear that the patient is suffering from delusions, hallucinations or both. He may demonstrate disorganized speech jumping from one concept to another with no association between the concepts, suggesting a looseness of associations within the stream of thought processes. These patients are psychotic; in psychiatric terminology they may be described as having positive signs of schizophrenia and will be normally classified according to the DSM as suffering from one or the other types of schizophrenia. Cognitively the patient may show concrete thinking or over-abstract conceptualizations. This is evident by their responses to proverbs and category assessments that show fluctuations and inconsistencies between concrete and over-abstract answers. Many of these patients proceed to a condition that has been called the "deficiency syndrome" or "negative signs of schizophrenia"; this is a debilitating condition where high mental functions such as volition and motivation are gone, the ability to feel emotions and intimacy and many of the personality traits flatten and fade away.

The scientific literature has repeatedly indicated that schizophrenia, especially "positive symptoms" and psychosis, is related to a disconnectivity syndrome (Friston 1995) pointing toward an etiology of connectivity imbalance in these patients (Peled 1999). Another direction taken to understand these debilitating syndromes is of consciousness as these patients actually show fragmentation and alteration of conscious experiences.

We have already mentioned the importance of connectivity dynamics for personality and internal representations and its relevance in experience dependent plasticity, thus it is understandable that "disconnection dynamics" or "over connection dynamics" can utterly destroy the brain functions and phenomena described so far. In addition to the dynamic connectivity organization achieved by the brain, - the brain is also hierarchical. Information processing in the brain proceeds hierarchically from lower –level unimodal (vision, auditory etc..) processes to higher-level multimodal associative processes such as auditory visual integration, and finally toward the higher most levels of global integrations the transmodal processing that integrate everything into a coherent experience (Mesulam 1998). Consciousness as a dynamic global process is composed from partial unconscious processes that become conscious by participating in the global process. This explains why conscious experience is serial while unconscious processes can proceed in Parallel (Barrs 1988). This formulation is in accordance with the idea of the hierarchical brain which at the transmodal higher levels achieves the emergent property of consciousness (Barrs 1988). Once formed, the higher levels of organization have a top-down control

influence over the information processes "traveling up" the hierarchy thus a certain hierarchical balance between bottom-up and top down processes is achieved by a well-organized brain.

The schizophrenia spectrum disturbances can be reconceptualized as disturbances to connectivity and hierarchical dynamics of the brain (Peled 1999). Disconnectivity dynamics will cause fragmentation of conscious experience. For example auditory experience can be dissociated from incoming auditory stimuli and from visual and other experiences and the patient will experience auditory hallucinations. Thought processes depending on the coherent connected activations of neuronal ensembles will become fragmented with jumps between concepts ensuing in loosening of associations. Illogical associations will create false assumptions about the environmental occurrences and these will bias understanding of events by aberrant top-down control, or shift, resulting in false unshakable beliefs explaining delusional ideation. If the brain system is disconnected and not stable, then typically the delusions will also be fragmented, changing and inconsistent. However, in cases of a more "pure" top-down shift when the brain networks are relatively stable and connected, a clinical picture of stable systemized delusion may take over.

The patient with poverty of speech and thought process, perseverating restricted to a reduced set of ideas and thoughts is activating over and over again a limited number of neural ensembles. As such he is having a reduced space of conceptions, and is suffering from over-connection dynamics where

overly-connected neuronal systems limit the activity of each other by constraining that activity to a few unchanged activations. Using models of neural networks (Geva & Peled 2000) it has been demonstrated how reduced activations have been caused by over-connectivity dynamics. Thus it can be concluded that patients with negative signs schizophrenia presumably suffer from over-connectivity dynamics. According to Meshulam (1998) volition is a result of higher level brain organizations, the transmodal systems, where volition is an emergent property of the integration of all sensation with action, i.e., sensory-motor integration. If higher-level brain organization is insufficient, or undeveloped, then the emergent property of volition and motivation will be lost. This is probably a major disturbance that patients with severe negative signs suffer from. The over-connectivity restricting neuronal network dynamics may hamper brain hierarchical formation, which explains why negative signs of avolition and poverty of thought typically occur in them.

Schizophrenia spectrum patients have a wide spectrum of clinical manifestations and the phenomena described above typically manifest in combinations with various disturbances predominating either at different times, or alternatively, together and continuously at different degrees. Thus, neuronal network disturbances occur to various degrees simultaneously. However some patterns of disease progressions have been identified. Many times the patients fluctuate between periods of predominant positive signs and periods of predominant negative signs. Typically the positive signs are more notable and present first in clinical settings. These fluctuations reflect

"oscillations" between disconnectivity and over-connectivity dynamics which probably take over many brain systems. In this regard schizophrenia spectrum disorder may be seen as a disturbance to some normal optimal connectivity balance in the brain. Tononi (1996) called this balance "neural complexity" indicating that for normal brain function optimal connectivity balance between disconnectivity and over-connectivity is warranted. In schizophrenia patients this optimal balance is lost. The disconnectivity dynamics is countered by corrective connectivity dynamics, that is possibly excessive and over-connectivity ensues. The system is plunged into oscillatory perturbation that results in an ever-deteriorating brain disturbance.

Section 4: Other patients with mixed conditions

The DSM has grown to include many more syndromes than those described so far, for example OCD (obsessive compulsive disorder) disorders of impulse control, PTSD (post traumatic stress disorder) dissociative disorders, dismorphophobia and anorexia nervosa. It is argued that these syndromes currently not described in the major sections fall into subtypes of the key disturbances above.

For example in OCD the main disturbance is that of repeating thoughts. Using neural network conceptualization repeating thoughts reflect re-activation of the same neuronal ensembles over and over again. If a thought or any other process (e.g., feeling or urge) is represented by a group of neuronal activation, and if that group of neurons is activated repeatedly again and again over time, then the thought, feeling or urge represented by that neural ensemble will repeat itself and reappear again and again. We have already seen that by strengthening the connections between groups of neurons these neurons tend to excite each other more than other neurons, and as a result they will reactivate each other repeatedly. In the case of OCD and other syndromes of repetition the neurons that are reactivated again and again represent the relevant phenomena being repeated. For example the neuronal ensemble of a specific thought is reactivated in OCD resulting in an obsession (i.e., intrusive repeated unpleasant thought), perseverations also act like this, and as we have seen, are typical to strengthening of connections in over-connectivity syndromes. This mechanism can explain a range of

psychiatric syndromes that have uncontrolled repetition of thoughts feelings and urges, for example "impulse control syndromes" where the urge for a certain action is repeated, or in PTSD where the activation of a certain memory is intrudingly repeated.

Dissociative disorders, dismorphophobia, anorexia nervosa and other similar syndromes, all have to do with distortion or split within conscious experience that biases familiarity and normal experience and creates misrepresentations of reality. In a sense it is a delusional-like process, or/and disconnection-like transmodal process but in minor severity. For example, in dissociative syndromes, parts of the conscious experience either distort or become unrelated to the rest of the experience or even completely disappear. Since the conscious experience is an emergent property of global brain organizations (that of transmodal formations Baars 1988, Mesulam 1998) such formations presumably suffer from disintegration where parts of the global organizations split off or loose the level of integration necessary for conscious experience. The major unique factor that characterizes anorexia nervosa is the distortion of body image (patients perceive themselves as fat when they are actually very slim). This distortion and others in dismorphophobia result from hierarchical brain imbalances; just like in systemized delusions, aberrant higher-level formations bias the perceptual incoming evidence from environmental occurrences.

We can deduce from the above that other DSM entities such as OCD, impulse control, PTSD dissociative disorders, dismorphohpobia and anorexia

nervosa are subtypes of the key disturbances in this manual because they constitute "Partial" disturbances, i.e., OCD, impulse control and PTSD are partial disturbances of overconnectivity dynamics. Dissociative disorders, dismorphohpobia and anorexia nervosa are partial disturbances of connectivity and hierarchical disturbances.

Section 5: Bedside assessment

As mentioned above, CBP can be used in its nominal form of novel brain-related taxonomy; which is appropriate for clinical settings e.g., for presentations of patients on the ward (use dictionary in Appendix 1). CBP can also be used in a more quantifiable vector-based version more suitable for research and administrative purposes (Appendix 2).

Table 2 summarizes CBP as a set of concise statements useful for consensual brain related taxonomy of descriptive clinical manifestations. First the symptomatic profile of the patients is obtained (Column 1) then according to Table 1 the patient is classified to the most relevant category, or to a set of concomitant categories (Column 2) related to his brain disturbance or set of disturbances. Accordingly Table 2 (below) generates for the patient an alternative brain-related taxonomy by which the patient's condition is expressed and conveyed. Appendix 1 is a dictionary that translates signs, symptoms and patient history into a patient-specific CBP formulation suitable or use at the bedside in the clinical settings.

The vector-based CBP formulation (Appendix 2) is built from all the major brain disturbances, they constitute the entries of the vector, thus the vector is constructed as follows DDMN, DMDD, DMDO, DMCO, ibDMCO, DD, TDS, OD, BUI (see Table 1 for details). As previously mentioned, each entry is a number representing the percentage of relevant symptoms manifestations from all possible symptoms signs and history findings of mental disorders. A

translation matrix (see Appendix 2) implemented with a computer program is available at the Neuroanalysis site, www.neuroanalysis.org.il.

Figure 1 gives two examples; for a psychotic and a depressed (dotted line) patient using CBP visualization vector graphs

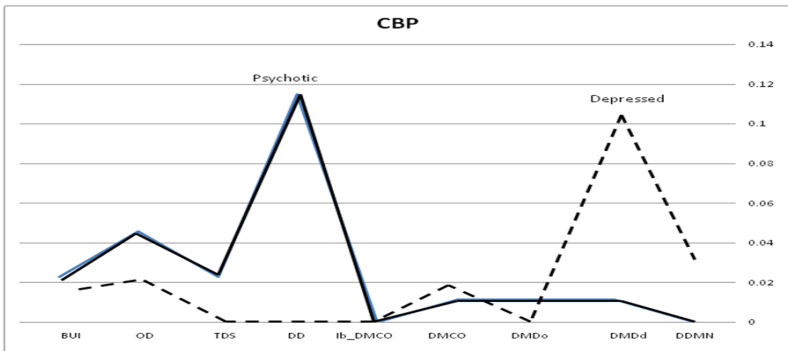


Table 2: Clinical Brain Profiling a rough outline

Descriptive Psychiatry	CBP Brain-related translation.
Personality disorders	Disturbances to the Default Mode Network organization and development DDMN
Depression	Disturbance of matching-dynamics of the de-optimized type (DMDd), mismatch dynamics dominates the brain-environment interactions.
Depression related to stress, adjustment reaction.	Disturbance of matching-dynamics of the de-optimized type due to environmental alteration (DMDd_ea)
Depression related to any factor that may reduce brain neural network efficiency.	Disturbance of matching-dynamics of the de-optimized type due to reduced neural resilience (DMDd_rnr)
Mania	Disturbance of matching-dynamics of the optimized type (DMDo), enhanced matching dynamics dominates the brain-environment interactions.
Bipolar	Oscillations between the two disturbances of matching dynamics (DMDdo)
Anxiety	Disturbance to multiple constraint organization (DMCO) distributed destabilization of neural network organizations.
Phobia	Input-bound disturbance to multiple constraint organization (ib_DMCO), distributed destabilization of neural network organizations due to certain external stimuli.
Disorganized, restless loose associations, disturbed logic, possible hallucinations. Delusions are disorganized.	Disconnection dynamics (DD), different brain systems and processes become statistically independent.
Delusional, stable organized delusions	Top-down shift, (TDS) higher-level of brain

	hierarchy, transmodal systems where schemata of internal representation form, bias incoming evidence from environment
Poverty of speech and thought, constricted affect, perseverating, limited conceptual space.	Over-connectivity dynamics (OD), different brain systems and processes constrain each other limiting the number of states in the brain system.
Avolition, lack of motivation, deficient function and cognition.	Bottom-up insufficiency (BUI), the highest-level of brain hierarchy, the transmodal systems, are lost or become deficient leaving the brain to function at lower-level organizations.
OCD (obsessive compulsive disorder) disorders of impulse control, PTSD (post traumatic stress disorder)	These are disorders where a group of neurons is activated repeatedly again and again over time; the activated neuronal groups represent thoughts feelings and urges according to the symptomatic manifestations. Partial Over-connectivity dynamics (pOD).
Dissociative disorders, dismorphobia and anorexia nervosa.	These are disorders of distortion or split within conscious experience, they are disintegrations where parts of the global organizations split off or loose their level of integration. These can also cause partial top-down effects similar to TDS phenomena. Partial Disconnection dynamics (pDD) and Top-down shift, (pTDS)

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Appendix

Appendix 1: DSM CBP dictionary.

The dictionary lists clinical findings on the left column, 1) signs (clinical findings on inspection according to mental status examination), 2) symptoms (these are patient complaints) and 3) history. Right column is a "diagnostic pointer" toward the presumed ethiopathology relevant to the clinical finding. The presumed ethiopathological brain disturbance becomes stronger if many clinical findings point to that disturbance. Different brain disturbances coexist and manifest together to certain extents according to the relevant clinical profile of the patient, thus each patient generates his own specific pattern of brain disturbance. The patient can have multiple concomitant disturbances some more dominant than others to different extents.

Clinical finding	CBP Neuroscientific hypothesis
Is the patient untidy or very messy?	This finding is non- specific it can indicate any major neuroscientific brain disturbance
Is the patient with excessive jewelry makeup and colored clothing?	Enhanced matching dynamics dominates the brain-environment interactions.
Moves slowly? Or even Stiff frozen?	Disturbance of matching-dynamics of the de-optimized type (DMDd), mismatch dynamics dominates the brain-environment interactions, but also Over-connectivity dynamics (OD), different brain systems and processes constrain each other limiting the number of states in the brain system, and Bottom-up insufficiency (BUI), the highest-level of brain hierarchy, the transmodal systems, are lost or become deficient
Restless, moves a lot? Or even Agitated looks as on verge of blowing up?	Non-specific, restless = Disturbance to multiple constraint organization (DMCO) distributed destabilization of neural network organizations. If more agitated than also = Disturbance of matching-dynamics of the optimized type (DMDo), enhanced matching dynamics dominates the brain-environment interactions, or/and also Disconnection dynamics (DD), different brain systems and processes become statistically

	independent.
Bizarre unexplainable movement?	Disconnection dynamics (DD), different brain systems and processes become statistically independent.
Repetitive stereotype movements?	Over-connectivity dynamics (OD), different brain systems and processes constrain each other limiting the number of states in the brain system.
Speaks slowly? And / or Limited verbal communication, gives short responses, few words only or none at all? And / or Speech at low tone or whisper	Disturbance of matching-dynamics of the de-optimized type (DMDd), mismatch dynamics dominates the brain-environment interactions, but also over-connectivity dynamics (OD), different brain systems and processes constrain each other limiting the number of states in the brain system, and bottom-up insufficiency (BUI), the highest-level of brain hierarchy, the transmodal systems, are lost or become deficient
Speaks fast? And / or Speaks a lot, gives long spontaneous responses?	Disturbance to multiple constraint organization (DMCO) distributed destabilization of neural network organizations, and /or disturbance of matching-dynamics of the optimized type (DMDo), enhanced matching dynamics dominates the brain-environment interactions. Sometimes also beginning of Disconnection dynamics
Speaks without stopping jumping from one issue to another? Speech with elevated tone?	Disturbance of matching-dynamics of the optimized type (DMDo), enhanced matching dynamics dominates the brain-environment interactions. And Disconnection dynamics (DD), different brain systems and processes become statistically independent.
Speech associations are loose; jumps from one sentence to another each different topic?	Disconnection dynamics (DD), different brain systems and processes become statistically independent.
Words are unrelated within sentences 'word salad'?	Higher degree of disconnection dynamics (DD), different brain systems and processes become statistically more independent.
Obsessions and compulsions?	Partial over-connectivity dynamics (OD), different brain

	systems and processes constrain each other activate each other again and again.
Repeating same topics of conversation?	Over-connectivity dynamics (OD), different brain systems and processes constrain each other limiting the number of states in the brain system.
Repeating /perseverating the same sentences? Responding to previous question?	Higher degree of Over-connectivity dynamics (OD), different brain systems and processes constrain each other limiting the number of states in the brain system.
Delusion, false unshakable belief? Stable as in Systemized delusion?	Top-down shift, (TDS) higher-level of brain hierarchy, transmodal systems where schemata of internal representation form, bias incoming evidence from environment
Delusion, false unshakable belief? Changing unstable	Top-down shift, (TDS) higher-level of brain hierarchy, transmodal systems where schemata of internal representation form, bias incoming evidence from environment together with Disconnection dynamics (DD), different brain systems and processes become statistically independent.
Illogical conclusions?	Disconnection dynamics (DD), different brain systems and processes become statistically independent.
Inappropriate affect?	Disconnection dynamics (DD), different brain systems and processes become statistically independent.
Flight of ideas	Disturbance of matching-dynamics of the optimized type (DMDo), enhanced matching dynamics dominates the brain-environment interactions.
Speech content includes mainly issues of despair, hopelessness, and pessimism.	Disturbance of matching-dynamics of the de-optimized type (DMDd), mismatch dynamics dominates the brain-environment interactions.
Speech content includes mainly issues of megalomania, over empowerment and unrealistic	Disturbance of matching-dynamics of the optimized type (DMDo), enhanced matching dynamics dominates the brain-environment interactions.

optimism (and plans)	
Bizarre or overly abstract response to categorization (proverbs) and abstraction?	Disconnection dynamics (DD), different brain systems and processes become statistically independent.
Concrete interpretation of proverbs and low abstraction?	Over-connectivity dynamics (OD), different brain systems and processes constrain each other limiting the number of states in the brain system.
Auditory hallucinations?	Disconnection dynamics (DD), different brain systems and processes become statistically independent.
Visual tactile olfactory hallucinations?	Disconnection dynamics (DD), different brain systems and processes become statistically independent with typical evidence for structural damage
Constricted affect and/ or Blunt affect?	Disturbance of matching-dynamics of the de-optimized type (DMDd), mismatch dynamics dominates the brain-environment interactions. In more ever cases of blunt affect can be / or also over-connectivity dynamics (OD), different brain systems and processes constrain each other limiting the number of states in the brain system. And /or bottom-up insufficiency (BUI), the highest-level of brain hierarchy, the transmodal systems, are lost or become deficient leaving the brain to function at lower-level organizations.
Expansive mood elevated affect?	Disturbance of matching-dynamics of the optimized type (DMDo), enhanced matching dynamics dominates the brain-environment interactions.
Dysphoric (suffering) affect?	Disturbance to multiple constraint organization (DMCO) distributed destabilization of neural network organizations. And /or disturbance of matching-dynamics of the de-optimized type (DMDd), mismatch dynamics dominates the brain-environment interactions.
Depressed affect?	Disturbance of matching-dynamics of the de-optimized type

	(DMDd), mismatch dynamics dominates the brain-environment interactions.
Anxious affect?	Disturbance to multiple constraint organization (DMCO) distributed destabilization of neural network organizations.
Detached from examiner?	Disturbance of matching-dynamics of the de-optimized type (DMDd), mismatch dynamics dominates the brain-environment interactions. And /or bottom-up insufficiency (BUI), the highest-level of brain hierarchy, the transmodal systems, are lost or become deficient leaving the brain to function at lower-level organizations.
Perplex ambivalent?	Disconnection dynamics (DD), different brain systems and processes become statistically independent.
Inappropriately close to examiner (no boundaries)?	Disturbance of matching-dynamics of the optimized type (DMDo), enhanced matching dynamics dominates the brain-environment interactions. And /or disturbances to the Default Mode Network organization and development DDMN
Suspicious with examiner? And /or Threatening to examiner?	Top-down shift, (TDS) higher-level of brain hierarchy, transmodal systems where schemata of internal representation form, bias incoming evidence from environment, and /or disturbances to the Default Mode Network organization and development DDMN
And /or the following Seductive toward examiner (theatrical)? Sensitive easily offended? Childish dependent regressive? Manipulating demanding? Stubborn obsessive non adaptable? Tend to idealize or devalue	Disturbances to the Default Mode Network organization and development DDMN (will typically cause mismatch dynamics MCO disturbances and in severe cases even temporary limited Disconnection dynamics, and top down shifts)

examiner? Egocentric un-empathic?	
Distractible? Disoriented? Memory loss?	Disconnection dynamics (DD), different brain systems and processes become statistically independent.
Complaints of Insomnia or hypersomnia?	Disturbance of matching-dynamics of the de-optimized type (DMDD), mismatch dynamics dominates the brain-environment interactions. And or / disturbance to multiple constraint organization (DMCO) distributed destabilization of neural network organizations.
Complaints of Early insomnia?	Disturbance to multiple constraint organization (DMCO) distributed destabilization of neural network organizations.
Complaints of Late insomnia?	Disturbance of matching-dynamics of the de-optimized type (DMDD), mismatch dynamics dominates the brain-environment interactions.
Complaints of Anorexia Wight loss	Partial Top-down shift, (TDS) higher-level of brain hierarchy, transmodal systems where schemata of internal representation form, bias incoming evidence from environment
Complaints of palpitations, dizziness, abdominal cramps and tingling. Complaints of anxiety fear of dying or loosing control panic	Disturbance to multiple constraint organization (DMCO) distributed destabilization of neural network organizations.
Complaints of fear of dying or loosing control panic in specific conditions.	Input-bound disturbance to multiple constraint organization (ib_DMCO), distributed destabilization of neural network organizations due to certain external stimuli.
Complaints of tension restlessness and agitation	Higher- levels of disturbance to multiple constraint organization (DMCO) distributed destabilization of neural network organizations.
Complaints of avolition indifference apathy	Bottom-up insufficiency (BUI), the highest-level of brain hierarchy, the transmodal systems, are lost or become deficient

Anhedonia	leaving the brain to function at lower-level organizations.
Complaints of depressed mood and / or Complaints of depressed mood especially in the morning	Disturbance of matching-dynamics of the de-optimized type (DMDd), mismatch dynamics dominates the brain-environment interactions.
Complaints about Flight of ideas?	Disturbance of matching-dynamics of the optimized type (DMDo), enhanced matching dynamics dominates the brain-environment interactions.
Complaints that things are strange unfamiliar changing not as usual (derealism depersonalization)	Disconnection dynamics (DD), different brain systems and processes become statistically independent.
Complaints of external control, mind reading, bugging, persecution (about delusions) and /or Complaints related to Systemized delusion	Top-down shift, (TDS) higher-level of brain hierarchy, transmodal systems where schemata of internal representation form, bias incoming evidence from environment
Complaints of low self esteem	Disturbances to the Default Mode Network organization and development DDMN and /or disturbance of matching-dynamics of the de-optimized type (DMDd), mismatch dynamics dominates the brain-environment interactions.
Complaints about being easily offended, oversensitive?	Disturbances to the Default Mode Network organization and development DDMN
Complaints of being impulsive, over imposing?	Disturbances to the Default Mode Network organization and development DDMN
History of Delusions?	Past top-down shift, (TDS) higher-level of brain hierarchy, transmodal systems where schemata of internal representation form, bias incoming evidence from environment

History of Hallucinations?	Past disconnection dynamics (DD), different brain systems and processes become statistically independent.
History of thought disorders loosening of associations	Past disconnection dynamics (DD), different brain systems and processes become statistically independent.
History of thought disorders perseverations poverty of thought?	Past over-connectivity dynamics (OD), different brain systems and processes constrain each other limiting the number of states in the brain system.
History of depressions?	Past disturbance of matching-dynamics of the de-optimized type (DMDd), mismatch dynamics dominates the brain-environment interactions.
History of mania?	Past disturbance of matching-dynamics of the optimized type (DMDo), enhanced matching dynamics dominates the brain-environment interactions.
History of anxiety	Past disturbance to multiple constraint organization (DMCO) distributed destabilization of neural network organizations.
History of phobias	Past input-bound disturbance to multiple constraint organization (ib_DMCO), distributed destabilization of neural network organizations due to certain external stimuli.
History of disturbed upbringing, parental loose and /or History of behavioral problems and / or History of coping deficiency work and social? And /or History of instable interpersonal relationships	Disturbances to the Default Mode Network organization and development DDMN
History of psychosocial or other stress (regular life stressors)	Disturbance of matching-dynamics of the de-optimized type due to environmental alteration (DMDd_ea)
History of trauma (stressor)	Disturbance of matching-dynamics of the de-optimized type

exceeding regular life stress)	due to environmental alteration (DMDD_ea) and possible partial Partial Over-connectivity dynamics (pOD).
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Appendix 2: CBP Matrix.

The left column lists all the clinical manifestations of mental disorders (see Reliability Table of Appendix 2). The top row lists the entries for the brain-related disturbances generated from the CBP matrix. CBP assessment is accomplished by scoring the number 1 in the yellow marked column. The scoring of #1 is related to finding the relevant corresponding clinical manifestation in the first column. The matrix translates clinical scores from the marked yellow column to numerical percentages for each type of brain-disturbance in the CBP vector of the first row in the table. For example, "the patient is untidy"(first row first column) is a general finding that can be relevant to many disturbances thus it is "spread" for nearly all of the first line, once scored as '1' it generates '1ns' for all the entries marked '0' in the matrix. "Childish dependent regressive" (9th row from bottom) is specific for DDMN thus it is not spread in its relevant row but is limited to scoring only the DDMN column.

Clinical	DDMN	DMDd	DMDo	DMCO	ib_DMCO	DD
Is the patient untidy?	0	0		0		0
Is the patient very messy?		0				0
Is the patient with excessive jewelry makeup and colored clothing?			0			
Moves slowly?		0				
Stiff frozen?		0				
Restless, moves a lot?			0	0		0
Agitated looks as on verge of blowing up?			0	0		0
Bizarre unexplainable movement						0
Repetitive stereotype movements?						
Speaks slowly?		0				
Limited verbal communication, gives short responses?		0				
Limited verbal communication, few words only or non at all		0				
Speech at low tone or whisper		0				
Speaks fast?			0	0		0
Speaks a lot, gives long spontaneous responses?			0			0
Speaks without stopping jumping from one issue to another?						0
Speech with elevated tone?			0	0		0
Speech associations are loose; jumps from one sentence to another each different topic?						0
Words are unrelated within sentences 'word salad'?						0
Repeating same topics of conversation?				0		0

Repeating /perseverating the same sentences?					0
Responding to previous question?					
Obsessions and compulsions?			0		
Delusion, false unshakable belief?					0
Systemized delusion?					
Illogical conclusions?					0
Inappropriate affect?					0
Flight of ideas		0			0
Speech content includes mainly issues of despair, hopelessness, and pessimism.	0	0			
Speech content includes mainly issues of megalomania, over empowerment and unrealistic optimism (and plans)			0		
Bizarre or overly abstract response to categorization (proverbs) and abstraction?					0
Concrete interpretation of proverbs and low abstraction?					
Auditory hallucinations?					0
Visual tactile olphactory hallucinations?					
Constricted affect			0		
Blunt affect?			0		
Expansive mood elevated affect?				0	
Dysphoric (suffering) affect?			0	0	
Depressed affect?			0		
Anxious affect?	0	0		0	0
Detached from examiner?		0			
Perplex ambivalent?					0
Inappropriately close to examiner (no boundaries)?			0		0
Suspicious with examiner?	0				0
Threatening to examiner?	0				0
Seductive toward examiner (theatrical)?	0		0		
Sensitive easily offended?	0				
Childish dependent regressive?	0				
Manipulating demanding?	0				
Stubborn obsessive non adaptable?	0				
Tend to idealize or devaluate examiner?	0				
Egocentric un-empathic?	0				
Distractible?	0		0	0	0
Disoriented?					0
Memory loss?					0
Complaints of Insomnia or hypersomnia?		0	0	0	0
Complaints of Early insomnia?				0	
Complaints of Late insomnia?		0			
Complaints of Anorexia Wight loss		0	0		
Complaints of palpitations, dizziness, abdominal cramps and tingling.					0

Complaints of anxiety fear of dying or loosing control panic			0		
Complaints of fear of dying or loosing control panic in specific conditions.				0	
Complaints of tension restlessness and agitation			0	0	0
Complaints of avolition indifference apathy Anhedonia	0				
Complaints of depressed mood	0				
Complaints of depressed mood especially in the morning	0				
Complaints about Flight of ideas?		0			0
Complaints that thing are strange unfamiliar changing not as usual (dereisim depersonalization)					0
Complaints of external control, mind reading, bugging, persecution (about delusions)					0
Complaints related to Systemized delusion					
Complaints of low self esteem	0	0			
Complaints about being easily offended, oversensitive?	0				
Complaints of being impulsive, over imposing?	0				
History of Delusions?					0
History of Hallucinations?					0
History of thought disorders loosening of associations					0
History of thought disorders perseverations poverty of thought?					
History of depressions?	0				
History of mania?		0			
History of anxiety			0		
History of phobias				0	
History of disturbed upbringing, parental loose	0				
History of behavioral problems	0				
History of coping deficiency work and social?	0				
History of instable interpersonal relationships	0				
History of psychosocial or other stress (regular life stressors)	0		0	0	
History of trauma (stressor exceeding regular life stress)	0		0	0	
	0	0	0	0	0

Appendix 3: CBP definitions for reliability

In order to achieve the same reliability of the DSM, CBP must use a consensual definition for each clinical manifestation used to score the CBP vector. This table of Appendix 3 attempts to remain in consensual boundaries relying on currently existing definitions and scales [i.e., DSM, SANS⁽¹⁾ SAPS⁽²⁾ Hamilton Depression⁽³⁾ Hamilton Anxiety⁽⁴⁾ Holms Rahe ⁽⁵⁾ referenced at the end of the table]

Detected	Description for scoring
Is the patient untidy?	Appearance is somewhat disheveled i.e., greasy hair, dirty clothes as in 'Grooming and Hygiene' section (1)
Is the patient very messy	Subject's clothes, body and environment are dirty and foul smelling as in 'Grooming and Hygiene section' (1)
Is the patient with excessive jewelry makeup and colored clothing?	It is evident that the clothing makeup and jewelry are grossly exaggerated. Excessiveness is the criteria. This score should not be assigned to people who are well groomed.
Moves slowly?	Obvious decrease of motor activity at interview as described in level '2' of retardation on the Hamilton Depression Scale (3) together with reduction of usage of expressive body gestures as in 'Marked' level of 'Paucity of expressive gestures' in the section of 'Affective Flattening' (1).
Stiff or frozen?	Subject never gesticulates as in 'Severe' rating of 'Paucity of expressive gestures' in the section of 'affective flattening' (1). In addition motor activity is reduced as rated for 'stupor' in the 'retardation' item of the Hamilton Depression Scale.
Restless, moves a lot?	As in 'Fidgets' in the 'Behavior at interview' score according to the Hamilton Anxiety scale (4) the patient finds it difficult to

	remain seated during the interview, moves a lot in the chair, moves arms legs, changes position often, he is 'Restless' as in the 'Tension' score (4).
Agitated looks as if on verge of "exploding"?	As in 'Paces' in the 'Behavior at interview' score according to Hamilton Anxiety scale (4) looks as if making the effort to restrain himself from becoming violent. Finds it hard to remain seated during the interview.
Bizarre unexplainable movement	Makes movements that are bizarre and non-purposeful, to the extent that they must be effortlessly noticed as such by interviewer and others. If the movements are explainable and their oddity is questionable then this item must not be scored as 'present'
Repetitive stereotype movements?	Movements that are repeated in the same (similar) manner; they can be 'repetitive stereotyped behavior' at the 'marked' level of the SANS (1)
Speaks slowly?	Speech is slow, words are pronounced slowly and pauses between words are longer than usual, speech must be slower than those who speak slowly. It should be easily and readily evident for the examiner, if there is doubt then this item must not be scored.
Limited verbal communication, gives short responses?	Restriction in the amount of spontaneous speech as in 'Alogia' section of the SANS (1) answers in single words or very short sentences, no spontaneous speech; the interview takes the form of investigation where the examiner repeatedly asks questions and the patient responds only briefly.
Limited verbal communication, few words only or non at all	Restriction in the amount of spontaneous speech as in 'Alogia' section of the SANS (1) Subject says almost nothing and frequently fails to answer.
Speech at low tone or whisper	'Lack of Vocal inflection' speaks in monotone, as in 'affective flattening' section of SANS (1). In addition voice is distinguishably weak

<p>Speaks fast?</p>	<p>Sentences are uttered rapidly - word follows word immediately. All speech is distinguishably fast more than the regular higher spectrum of normal speech. It should be easily and readily evident for the examiner, if there is doubt, this item should not be scored.</p>
<p>Speaks a lot, gives long spontaneous responses?</p>	<p>Here the emphasis is on the volume of speech (rather than speed), the patient starts to speak continuously even when not asked any questions, once starting he never ends and it is difficult to stop him or insert a question while he is speaking).</p>
<p>Speaks without stopping, jumps from one issue to another?</p>	<p>In addition to the description of the above previous score, here the patient is practically unstoppable and speech content is disturbed in the sense that jumping from one concept to unrelated (or loosely related) concepts is the rule.</p>
<p>Speech with elevated tone?</p>	<p>Tone is elevated to the extent that the patient seems to be shouting. The tone is higher than the normal range of voice tones, if there is doubt then this item should not be scored.</p>
<p>Speech associations are loose; jumps from one sentence to another each a different topic?</p>	<p>As in 'Marked Derailment' of the SAPS (2) 'Frequent instances of derailment: subject is often difficult to follow' only 'Marked' levels warrant a score here, 'Moderate' and 'Mild' do not.</p>
<p>Words are unrelated within sentences 'word salad'?</p>	<p>As in 'Severe Derailment' of the SAPS (2) 'Derailment so frequent and / or extreme that the subject's speech is almost incomprehensible' Here also the 'Marked and Severe Incoherence' items of the SAPS (2) apply, 'At least half of the subject's speech is incomprehensible'.</p>
<p>Repeating same topics of conversation?</p>	<p>The patient is pre-occupied by a set of thoughts and repeatedly expresses them in speech. Typically this is expressed in conversation; no matter where the examiner takes the topics of discussion, the patient inevitably returns to his set of concerns. The examiner cannot divert the patient from his repeated issues for long and the patient returns to his original thoughts.</p>

Repeating/perseverating the same sentences?	Here sentences are concretely repeated over and over again
Responding to previous question?	The patient is 'stuck' answering the first question although other additional questions were already asked. For example what is your name? John, where do you live? John... and so on
Obsessions and compulsions?	As in DSM
Delusion, false unshakable belief?	As in all delusions of the 'Delusions' chapter of the SAPS (2) rated 'Moderated' 'Marked' or 'Severe'
Systemized delusion?	Delusion is non-bizarre stable over time tends to grow incorporating new events in the experience of the patient. As in the Delusional disorder of the DSM.
Illogical conclusions?	As in 'Illogicality' SAPS (2) rated 'Moderated' 'Marked' or 'Severe'
Inappropriate affect?	As in 'Inappropriate affect' SAPS (2) rated 'Moderate' 'Marked' or 'Severe'
Flight of ideas	As in 'Pressure of speech ' SAPS (2) rated 'Moderate' 'Marked' or 'Severe'
Speech content includes mainly issues of despair, hopelessness, and pessimism.	As in Hamilton depression scale (3) items 'Guilt,' 'Helplessness,' 'Hopelessness' and 'Worthlessness' - scores 1 to 4
Speech content includes mainly issues of megalomania, over empowerment and unrealistic optimism (and plans)	The subject is concerned with issues of megalomania, over empowerment and unrealistic optimism (and plans). This must be self-evident and obvious.
Bizarre or overly abstract response to categorization	Bizarre or overly abstract response to categorization (proverbs) and abstraction

(proverbs) and abstraction?	
Concrete interpretation of proverbs?	Concrete interpretation of proverbs for example the common characteristic of table chair and cupboard are that they are made of wood instead of that they are all furniture. Concrete responses are given even after assisting the patient with examples of abstraction from related issues - for example "apple banana orange are fruit"
Auditory hallucinations?	As in 'Auditory Hallucinations' including voices commenting and conversing of the SAPS (2) rated 'Mild' 'Moderate' 'Marked' or 'Severe'
Visual tactile olphactory hallucinations?	As in the other 'Hallucinations' Visual tactile and olphactory of the SAPS (2) rated 'Mild' 'Moderate' 'Marked' or 'Severe'
Constricted affect	As in 'Unchanging facial expression' in the SANS (1) 'Moderate: Subject's expressions are dulled overall, but not absent' and "Marked: Subject's face has a flat 'set' look, but flickers of affect arise occasionally"
Blunt affect?	As in 'Unchanging facial expression' in the SANS (1) "Severe: Subject's face looks 'wooden' and changes little, if at all throughout the interview".
Expansive mood elevated affect?	The subject seems elated overly happy, mood is excessive in a self-evident unquestionable manner.
Dysphoric (suffering) affect?	Facial expression of suffering; uneasy as in an uncomfortable state of mind. Must be evident, if questionable no score is applied.
Depressed affect?	Facial expression is of painful sadness (typical triangle form of eyebrow). Must be evident, if questionable no score is applied.
Anxious affect?	Facial expression is of anxious form, constricted facial muscles, and bulging eye expression. Startled and / or crying expression. Must be evident, if questionable no score is applied

Detached from examiner?	The patient behaves as if the examiner (and others), are not there, seems to be reflecting on inner thoughts and is not available for whatever is occurring in the interview or around him. Must be evident, if questionable no score is applied.
Perplexed, ambivalent?	Face expression is similar to that of a person seeing something extraordinary for the first time, and seems to be lost, not knowing where to turn. Must be evident, if questionable no score is applied.
Inappropriately close to examiner (no boundaries)?	Attitude toward the examiner is as if he were a 'buddy' of the patient or a close intimate relative. Asks intimate embarrassing intruding questions, sits close to the examiner (may touch or hug him). Must be evident, if questionable no score is applied
Suspicious with examiner?	Suspicious attitude toward the examiner as if the examiner is a threat, or wants to harm the patient. Must be evident, if questionable no score is applied.
Threatening to examiner?	Seems as if about to get up and hit the examiner. Must be evident, if questionable no score is applied.
Seductive toward examiner (theatrical)?	Attitude toward the examiner is as if he were a 'buddy' of the patient or a close intimate relative but with a seducing actively probing attitude. Must be evident, if questionable no score is applied.
Sensitive easily offended?	Overly reactive easily offended, tends to respond to regular instructions as if they were harsh criticism. Must be evident, if questionable no score is applied.
Childish dependent regressive?	Attitude of the patient gives an impression of a little child, with childish facial expression and intonation of speech. Needs instructions and guidance even for simple tasks. Must be evident, if questionable no score is applied.
Manipulating demanding?	The examiner senses a constant uneasy feeling of being pressed or utilized to say, feel or do uncomfortable things. Must be evident, if questionable no score is applied.

Stubborn, obsessive non adaptable?	Attitude to examiner and other events are obstinate, inflexible, and repeatedly insisted upon. Must be evident, if questionable no score is applied.
Tend to idealize or devalue examiner?	Attitude to the examiner as if he is the most wonderful and best therapist in the world, or the worst person ever; these attitudes can interchange frequently. Must be evident, if questionable no score is applied.
Egocentric un-empathic?	Thinks of no one but himself, unable to see the view point of others, cannot put himself in "others shoes" Must be evident, if questionable no score is applied.
Distractible?	Every stimulus from the environment causes the subject to turns his attention from the main course of the interview. Must be evident, if questionable no score is applied.
Disoriented?	Unable to orient himself, does not know the time and day, may not recognize faces of relatives.
Memory loss?	Unable to remember things of recent past days and weeks. Recall is typically preserved and long term memory is typically present
Complaints of Insomnia or hypersomnia?	Insomnia or hypersomnia
Complaints of Early insomnia?	Early insomnia, hard to fall asleep
Complaints of Late insomnia?	Late insomnia, early wake
Complaints of Anorexia Wight loss	Anorexia, Weight loss
Complaints of palpitations, dizziness, and / or abdominal cramps and / or tingling.	Palpitations, dizziness, and / or abdominal cramps and / or tingling.

Complaints of anxiety fear of dying or loosing control panic	Fear of dying or loosing control panic
Complaints of fear of dying or loosing control panic in specific conditions.	Fear of dying or loosing control; panic in specific conditions.
Complaints of tension, restlessness and agitation	Tension, restlessness and agitation
Complaints of avolition indifference apathy Anhedonia	Avolition, indifference, apathy, anhedonia
Complaints of depressed mood	Being sad as in the Hamilton Depression Scale items and major depression
Complaints of depressed mood especially in the morning	Being sad as in the Hamilton Depression scale items and major depression especially in the morning
Complaints about Flight of ideas?	Head full of racing thoughts
Complaints that things are strange and unfamiliar - changing not as usual (dereisim? depersonalization)	A sense that something is not usual, there are hidden meanings to things, there are forces acting behind things, things are connected in a meaningful way to the individual. Must be evident, if questionable no score is applied.
Complaints of external control, mind reading, bugging, persecution (about delusions)	Feeling as if controlled by external sources, others can read his mind; he is being persecuted. others intend and plan to hurt him. Must be evident, if questionable no score is applied
Complaints related to	There is a dominating non-bizarre false idea that gradually

Systemized delusion	grows and incorporates all occurrences and aspects of life. Must be evident, if questionable no score is applied
Complaints of low self esteem	Feeling worthless.
Complaints about being easily offended, oversensitive?	Easily offended, oversensitive to criticism and insinuations. Interprets even the slightest inattention from others as rejection and humiliation. Must be evident, if questionable no score is applied.
Complaints of being impulsive, over imposing?	Reacts immediately without giving it another thought, unable to change the decision or reaction once taken. Must be evident, if questionable no score is applied
History of Delusions?	As above
History of Hallucinations?	As above
History of thought disorders loosening of associations	As above
History of thought disorders perseverations poverty of thought?	As above
History of depressions?	As in DSM criteria
History of mania?	As in DSM criteria
History of anxiety	As in DSM criteria
History of phobias	As in DSM criteria
History of disturbed upbringing, parental loose	Parents were not available (or orphan) the family history is of turmoil, instability and frequent changes. Subject deprived of needed attention care and love, or / and abused maltreated. Must be evident from anamnesis, if questionable no score is applied
History of behavioral problems	Problems at school, patient often reprimanded in school because of misbehavior, must be more than regular child's mischief; later problems with the law are typical. Must be evident from

	anamnesis, if questionable no score is applied
History of inability to maintain employment and social relationships?	Unable to remain employed for an extended period of time, interpersonal relationships. Are generally short and unstable; and frequently changes partners. Must be evident from anamnesis, if questionable no score is applied.
History of unstable interpersonal relationships	Interpersonal relationships chaotic, characterized by turmoil. Must be evident from anamnesis, if questionable no score is applied.
History of psychosocial or other stress (regular life stressors)	As in Holmes-Rahe life changes scale (5): Changes to different line of work, Change in number of arguments with spouse, Mortgage over \$100,000, Foreclosure of mortgage or loan, Change in responsibilities at work, Son or daughter leaving home, Trouble with in-laws, Outstanding personal achievement, Wife begins or stops work, Begin or end school, Change in living conditions, Revision in personal habits, Trouble with boss, Change in work hours or conditions, Change in residence, Change in schools, Change in recreation, Change in church activities, Change in social activities, Mortgage or loan less than \$30,000, Change in sleeping habits, Change in number of family get-togethers, Change in eating habits, Vacation, Christmas alone, Minor violations of the law.
History of trauma (stressor exceeding regular life stress)	As in Holmes-Rahe life changes scale (5): Death of spouse, Divorce, Martial separation, Jail term, Death of close family member, Personal injury or illness Marriage, Fired at work, Marital reconciliation, Retirement, Change in health of a family member, Pregnancy, Sex Difficulties, Gain of new family member, Business readjustment, Change in financial state, Death of close friend

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